

2-Chlorodeoxyadenosine (2-CDA) for the Treatment of Refractory or Recurrent Langerhans Cell Histiocytosis (LCH) in Pediatric Patients

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Background. Pediatric patients with Langerhans cell histiocytosis (LCH) may become refractory to conventional therapy or present with repeated recurrences over several years. Current therapeutic options such as prednisone, vinblastine, etoposide, and cyclosporine are associated with significant acute toxicities and late effects. Recent reports suggested that 2-chlorodeoxyadenosine (2-CDA) may be an effective agent in adults with LCH. The purpose of this study was to determine the safety and efficacy of 2-CDA in children with LCH.

Methods. This report presents the data collected from the first three patients that have completed this trial. Patients were enrolled in a prospective study after informed consent was obtained. Patients had a confirmed diagnosis of LCH that had recurred several times or not responded to standard therapy. Patients were given a starting dose of 5 mg/M2 of daily con-

tinuous infusion for three days duration. Two patients had their dose increased to 6.5 mg/M2/day. A total of 4–6 courses were given, and courses were repeated every 3–4 weeks. Thirteen of fifteen courses were given as outpatients at home.

Results. Each patient completed therapy with myelosuppression the primary toxicity. Pt. 1 initially received a higher dose of 2-CDA and developed sepsis. The dose was reduced to current study levels and no other incidence of infection, fever, and neutropenia, or blood product transfusion was required. All three patients are free of active disease 10–18 months after completing 2-CDA.

Conclusion. Three patients with LCH refractory to standard therapy had CR to 2-CDA, given at 5–6.5 mg/M2/day for 3 days, without significant toxicity. Med. Pediatr. Oncol. 29:288–292, 1997. © 1997 Wiley-Liss, Inc.

Key words: Langerhans cell histiocytosis (LCH); 2-chlorodeoxyadenosine (2-CDA); pediatrics

INTRODUCTION

Children with Langerhans cell histiocytosis (LCH) may have a varied presentation. The number and severity of organs affected, age of the patient, and number of recurrences all appear to have a significant impact on the prognosis of LCH. Some children respond to mild short term immunosuppressive agents including prednisone, vinblastine, methotrexate, 6-mercaptopurine, etoposide, and cyclosporine [1–3]. However, there is a population of patients at risk for recurrent or refractory disease. These patients require long-term immunosuppression and are thus prone to develop side effects including growth arrest, glucose intolerance, obesity, recurrent infections, liver dysfunction, and renal impairment. Therefore, an effective treatment for LCH that is relatively short with minimal toxicity is needed. Recent reports suggested that 2-CDA may have an impact on patients with LCH [4,5]. We have begun a prospective regimen of outpatient continuous intravenous infusion 2-CDA in children with LCH to determine the response rate and toxicities. We present the first three patients to complete this therapy at our institution.

METHODS

All three patients had a biopsy confirmed diagnosis of LCH including special stains for S-100 and when possible electron micrographs to document the presence of Birbeck's granules. Informed consent was obtained prior to starting 2-CDA. 2-CDA was administered at the dosage indicated as a continuous infusion by portable pump. Courses were repeated every 3–5 weeks when blood counts had recovered from the previous course. All previous therapy for LCH was administered similar to previous recommended and published doses and schedules.

RESULTS

Patient 1 was 2.9 years of age at initial diagnosis of LCH. She presented with recurrent otitis media and ex-

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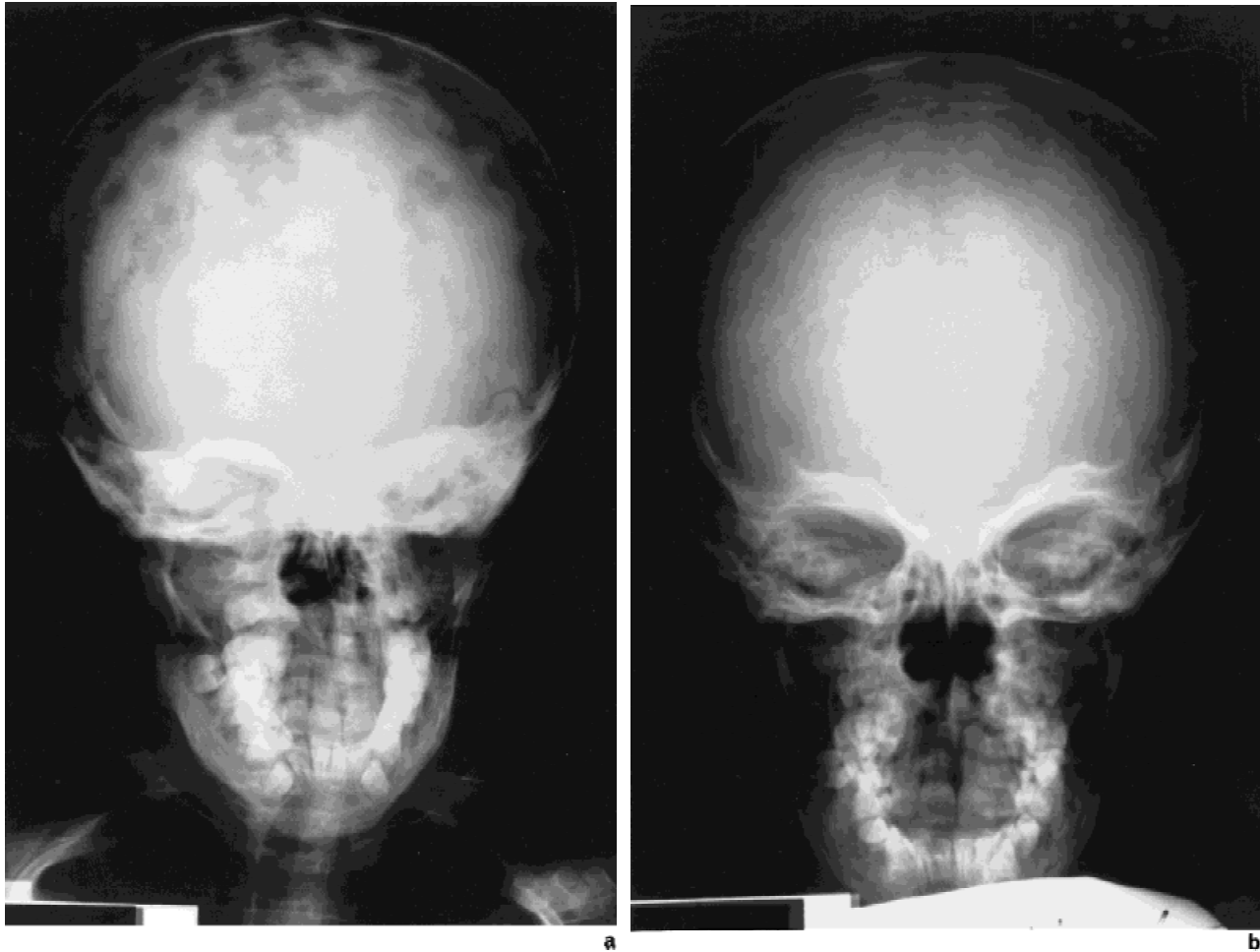


Fig. 1. Radiographs of skull of Pt. 1 prior to 2-CDA (a), and 4 months after completing 2-CDA (b)

terna, anemia, hepatosplenomegaly, lytic bone disease of the skull, and a seborrheic dermatitis involving more than 50% of the scalp for more than 6 months duration. She was treated with multiple courses of prednisone and vinblastine, followed by oral etoposide, and eventually prednisone and cyclosporine for multiple episodes of recurrent/progressive disease. After 3 years of therapy her height was well below the 5th percentile. She returned again with significantly worsened skin rash, more than 30 lytic lesions in the skull (Figure 1a), an enlarging liver, splenomegaly to the level of the umbilicus, and anemia with an elevated reticulocyte count. She was started on 2-CDA and received a total of 4 courses. Her first course was given at a dose of 8 mg/M²/day continuous infusion (CI) for 5 days. This course was followed by fever, neutropenia, and bacteremia. Duration of neutropenia was 3 weeks. Subsequent courses were reduced to 5 mg/M²/day \times 3 days (CI); this course was repeated every 3–4 weeks for a total of 3 courses at this dose. She did not require further blood product support nor did she develop fever and neutropenia. She has been off therapy

now for 18 months, with a normal hemoglobin and hematocrit, and resolution of her skull lesions (Figure 1b), dermatitis, and hepatosplenomegaly.

Patient 2 was 1.5 years of age at diagnosis when she presented with hilar and abdominal lymphadenopathy and bony disease. She received repeated courses of vinblastine and prednisone, and subsequently cyclosporine, for multiple recurrences. Prior to initiation of 2-CDA, she presented with exophthalmus, anemia, somnolence, and diabetes insipidus. An MRI revealed soft tissue and bony involvement in her orbit and face, and a large infundibular mass (Fig. 2a). She received 6 courses of 2-CDA (CI) at 4 week intervals (maximum dose of 6.5 mg/M²/day \times 3 days) without complications. Her primary toxicity was myelosuppression with a nadir of 400 in the absolute neutrophil count after courses 3–6, with duration of neutropenia less than 7 days with courses 3, 4, 5, and less than 2 weeks with course 6. Her platelet count was always greater than 200,000. She has been off therapy for 12 months without evidence for disease. A repeat CT four months off therapy showed the intracra-



Fig. 2. MRI of infundibular mass prior to 2-CDA (a) and a CT of same lesion 6 months after completing therapy (b). Arrow denotes lesion site.

nial lesion to be nearly resolved (Fig. 2b), resolution of the orbital soft tissue lesion, and healing of all bony lesions.

Patient 3 was an 18-year-old female with multiple recurrences of bony disease over the past seven years. She also had received multiple courses of prednisone and vinblastine, and later etoposide. After her most recent relapse of skull lesions (Figure 3) she received 5 courses of 2-CDA (CI) scheduled at 4 week intervals. Her ANC nadir was 1400, and her WBC nadir was 2.4 with a duration of less than one week after course 4. She is now 14 months off therapy without evidence of disease.

DISCUSSION

Langerhans cell histiocytosis (LCH) has a varied presentation and course in children. Often, LCH can be treated with minimal surgery, localized therapy, or a 3–4 month course of mild immunosuppression with agents such as prednisone, vinblastine, methotrexate, or 6 mercaptopurine. However, some patients have refractory disease requiring multiple courses of therapy and changes in the type of therapy [1,6,7]. Recently, investigators have examined the role of alpha interferon, cyclosporine, and most recently 2-CDA [3,4,5]. The three pediatric patients we presented had received a minimum of 3 years of prior therapy but continued to have relapses. Patients 1 and 2 were ages 2.9 and 1.5 y.o. at diagnosis and had developed

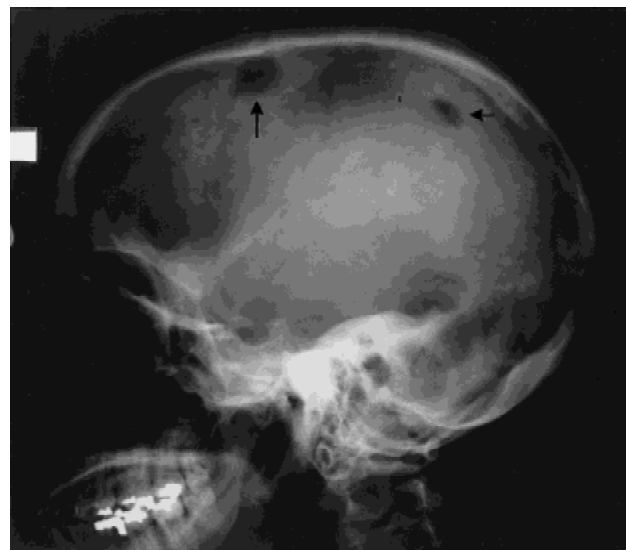


Fig. 3. Skull radiographs of Pt.3 prior to 2-CDA.

marked growth arrest due to the recurrent use of steroids and other cytotoxic therapy. 2-CDA therapy was well tolerated. There were no complaints of nausea, vomiting, headaches, myalgias, or fever during the infusions. The patients were treated as outpatients using a portable continuous infusion pack.

All three patients had excellent clinical and radiographic responses. Patients 1 and 2, who would be classified by the system of Egler and D'Angio as having

extensive disease with organ dysfunction, have had CR of durations of 18 and 12 months, respectively, compared to their longest previous CR's of 6 and 4 months. Additionally, each patient had significant improvement in weight gain and height velocity. Pt. 1. had a predicted height velocity (HV) prior to 2-CDA of 6.8 cm/yr compared to an actual HV of 2.8 cm/yr. After 2-CDA, her predicted value was 5 cm/yr, but her actual HV was 8 cm/yr. The predicted HV for Pt. 2 prior to 2-CDA was 10 cm/yr with an actual HV of 5 cm/yr. After 2-CDA, her actual height velocity was 10 cm/yr compared to a predicted of 6 cm/yr. Pt. 3 would be classified as having restricted disease with polyostotic involvement [1]. It is believed that those patients with more extensive disease are at greater risk for recurrences or complications due to LCH [8,9].

The use of 2-CDA has been reported in adults with refractory LCH [4]. The clinical response of LCH to 2-CDA correlates with *in vitro* data suggesting that monocytes and macrophages, presumably the cells of origin of LCH, are exquisitely sensitive to 2-CDA. Additionally, patients treated with 2-CDA experience a rapid fall in their circulating monocyte count [10,11].

The response of the bony lesions to 2-CDA was similar to responses reported with other therapies [12]. These lesions developed sclerotic changes after 2 courses and continued to resolve 2–4 months after the last course of 2-CDA was administered. Thus, it is important to continue monitoring these patients for slow and continued resolution of their bony disease, and to not resume therapy unless there is clear evidence for progressive disease.

The response rate in this series of patients and the lack of serious toxicity, support continued investigation of 2-CDA as a potential drug of choice for initial relapse in LCH, or perhaps as front-line therapy in aggressive disease. Other recently described relapse therapies have several disadvantages compared to 2-CDA. Etoposide has shown some benefit in patients with LCH especially those with diabetes insipidus [13,14]. However, there is concern about the risk of developing a secondary myeloid malignancy after the use of etoposide [15]. Alpha interferon is another outpatient based treatment regimen studied in patients with LCH. Although it is easy to administer, it requires multiple injections and has significant systemic symptoms associated with its use. Cyclosporine (CSA) has recently been highlighted as an alternative therapy for patients with recurrent or refractory LCH [3]. Patient 1 had been on CSA for over 8 months and still developed progressive disease. CSA is also associated with unique problems including renal and liver toxicity and lymphoproliferative disease [16].

Ladisch and Gadner have reviewed many of the previously published treatment trials for LCH. These authors highlight the need for cooperative group trials and

more consistent stratification and outcome measures. More importantly they describe the role of the Histiocyte Society in the development and implementation of a front-line international study of newly diagnosed patients with LCH (LCH-1). The treatment outline uses the concept of risk-directed therapy. If the patient has a poor response, they were able to switch treatment arms. The authors note that those with multi-system involvement and a poor response at six weeks were then eligible for a Salvage Protocol. This protocol offers a choice between CSA and anti-thymocyte globulin or marrow ablative therapy with allogeneic bone marrow transplantation [17]. The work of the Histiocyte Society in the promotion of these treatment protocols is vital. North American investigators need to be aware of the Society's work and treatment protocols. 2-CDA may be an appropriate agent to place in a salvage therapy study by the Histiocyte Society.

CONCLUSION

2-CDA therapy resulted in CR in 3 heavily pre-treated patients with LCH. Therapy was easily administered, with no significant immediate or delayed toxicity. Further clinical trials are necessary to determine the role of 2-CDA in relapse or high-risk front-line LCH therapy, and to determine the optimal dosage form (IV or oral) and dosing schedule.

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